

We claim:

1. A peptide compound of the formula [I] [SEQ. ID. NO. 4]:

Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Ala Xaa<sub>19</sub> Xaa<sub>20</sub>  
Xaa<sub>21</sub> Xaa<sub>22</sub> Xaa<sub>23</sub> Xaa<sub>24</sub> Xaa<sub>25</sub> Xaa<sub>26</sub> Xaa<sub>27</sub> Xaa<sub>28</sub>-Z<sub>1</sub>; wherein

Xaa<sub>1</sub> is His, Arg, Tyr, Ala, Norval, Val  
or Norleu;

Xaa<sub>2</sub> is Ser, Gly, Ala or Thr;

Xaa<sub>3</sub> is Ala, Asp or Glu;

Xaa<sub>4</sub> is Ala, Norval, Val, Norleu or Gly;

Xaa<sub>5</sub> is Ala or Thr;

Xaa<sub>6</sub> is Phe, Tyr or naphthylalanine;

Xaa<sub>7</sub> is Thr or Ser;

Xaa<sub>8</sub> is Ala, Ser or Thr;

Xaa<sub>9</sub> is Ala, Norval, Val, Norleu, Asp or Glu;

Xaa<sub>10</sub> is Ala, Leu, Ile, Val, pentylglycine or Met;

Xaa<sub>11</sub> is Ala or Ser;

Xaa<sub>12</sub> is Ala or Lys;

Xaa<sub>13</sub> is Ala or Gln;

Xaa<sub>14</sub> is Ala, Leu, Ile, pentylglycine, Val or Met;

Xaa<sub>15</sub> is Ala or Glu;

Xaa<sub>16</sub> is Ala or Glu;

Xaa<sub>17</sub> is Ala or Glu;

Xaa<sub>19</sub> is Ala or Val;

Xaa<sub>20</sub> is Ala or Arg;

Xaa<sub>21</sub> is Ala or Leu;  
 Xaa<sub>22</sub> is Phe, Tyr or naphthylalanine;  
 Xaa<sub>23</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;  
 Xaa<sub>24</sub> is Ala, Glu or Asp;  
 Xaa<sub>25</sub> is Ala, Trp, Phe, Tyr or naphthylalanine;  
 Xaa<sub>26</sub> is Ala or Leu;  
 Xaa<sub>27</sub> is Ala or Lys;  
 Xaa<sub>28</sub> is Ala or Asn;  
 Z<sub>1</sub> is -OH,

-NH<sub>2</sub>,

Gly-Z<sub>2</sub>,

Gly Gly-Z<sub>2</sub>

Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub> or

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub> Xaa<sub>39</sub>-Z<sub>2</sub>;

wherein

Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently  
 selected from the group consisting of Pro,  
 homoproline, 3Hyp, 4Hyp, thioproline,  
 N-alkylglycine, N-alkylpentylglycine and  
 N-alkylalanine; and

Z<sub>2</sub> is -OH or -NH<sub>2</sub>;

provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>4</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>,  
 Xaa<sub>9</sub>, Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>,

Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub>, and Xaa<sub>28</sub> are Ala; and provided also that, if Xaa<sub>1</sub> is His, Arg or Tyr, then at least one of Xaa<sub>3</sub>, Xaa<sub>4</sub> and Xaa<sub>9</sub> is Ala; and pharmaceutically acceptable salts thereof;

2. A compound according to claim 1 wherein Xaa<sub>1</sub> is His, Ala or Norval.

3. A compound according to claim 1 wherein Xaa<sub>1</sub> is Ala.

4. A compound according to claim 2 wherein Xaa<sub>1</sub> is Ala.

5. A compound according to claim 1 wherein Xaa<sub>1</sub> is His.

6. A compound according to claim 2 wherein Xaa<sub>1</sub> is His.

7. A compound according to claim 1 wherein Xaa<sub>2</sub> is Gly.

8. A compound according to claim 2 wherein Xaa<sub>2</sub> is Gly.

9. A compound according to claim 1 wherein Xaa<sub>3</sub> is Ala.

10. A compound according to claim 2 where Xaa<sub>3</sub> is Ala.

11. A compound according to claim 1 wherein Xaa<sub>4</sub> is Ala.

12. A compound according to claim 2 where Xaa<sub>4</sub> is Ala.

13. A compound according to claim 1 wherein Xaa<sub>9</sub> is Ala.

14. A compound according to claim 2 where Xaa<sub>9</sub> is Ala.
15. A compound according to any of claims 8-14 wherein Xaa<sub>14</sub> is Leu, pentyglycine or Met.
16. A compound according to claim 15 wherein Xaa<sub>25</sub> is Trp or Phe.
17. A compound according to claim 16 wherein Xaa<sub>6</sub> is Ala, Phe or naphthylalanine; Xaa<sub>22</sub> is Phe or naphthylalanine; and Xaa<sub>23</sub> is Ile or Val.
18. A compound according to claim 17 wherein Z<sub>1</sub> is -NH<sub>2</sub>.
19. A compound according to claim 17 wherein Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.
20. A compound according to claim 1 wherein Xaa<sub>39</sub> is Ser or Tyr.
21. A compound according to claim 17 wherein Xaa<sub>39</sub> is Ser or Tyr.
22. A compound according to claim 1 wherein Xaa<sub>39</sub> is Ser.
23. A compound according to claim 17 wherein Xaa<sub>39</sub> is Ser.

24. A compound according to claim 1 wherein  $Z_2$  is  $-NH_2$ .

25. A compound according to any of claims 19, 21 or 23 wherein  $Z_2$  is  $-NH_2$ .

26. A compound according to claim 1 wherein  $Z_1$  is  $-NH_2$ .

27. A compound according to claim 1 wherein  $Xaa_{31}$ ,  $Xaa_{36}$ ,  $Xaa_{37}$  and  $Xaa_{38}$  are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

28. A compound according to claim 1 which has an amino acid sequence selected from SEQ. ID. NOS. 5 to 93.

29. A peptide compound of the formula [I] [SEQ. ID. NO. 4]:

$Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13}$   
 $Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17} Ala Xaa_{18} Xaa_{19} Xaa_{20} Xaa_{21} Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25}$   
 $Xaa_{26} Xaa_{27} Xaa_{28}-Z_1$ ; wherein

$Xaa_1$  is His or Ala;

$Xaa_2$  is Gly or Ala;

$Xaa_3$  is Ala, Asp or Glu;

$Xaa_4$  is Ala or Gly;

$Xaa_5$  is Ala or Thr;

$Xaa_6$  is Phe or naphthylalanine;

$Xaa_7$  is Thr or Ser;

$Xaa_8$  is Ala, Ser or Thr;

Xaa<sub>9</sub> is Ala, Asp or Glu;  
Xaa<sub>10</sub> is Ala, Leu or pentylglycine;  
Xaa<sub>11</sub> is Ala or Ser;  
Xaa<sub>12</sub> is Ala or Lys;  
Xaa<sub>13</sub> is Ala or Gln;  
Xaa<sub>14</sub> is Ala, Leu, Met or pentylglycine;  
Xaa<sub>15</sub> is Ala or Glu;  
Xaa<sub>16</sub> is Ala or Glu;  
Xaa<sub>17</sub> is Ala or Glu;  
Xaa<sub>19</sub> is Ala or Val;  
Xaa<sub>20</sub> is Ala or Arg;  
Xaa<sub>21</sub> is Ala or Leu;  
Xaa<sub>22</sub> is Phe or naphthylalanine;  
Xaa<sub>23</sub> is Ile, Val or tert-butylglycine;  
Xaa<sub>24</sub> is Ala, Glu or Asp;  
Xaa<sub>25</sub> is Ala, Trp or Phe;  
Xaa<sub>26</sub> is Ala or Leu;  
Xaa<sub>27</sub> is Ala or Lys;  
Xaa<sub>28</sub> is Ala or Asn;  
Z<sub>1</sub> is -OH,  
-NH<sub>2</sub>,  
Gly-Z<sub>2</sub>,  
Gly Gly-Z<sub>2</sub>  
Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub>  
Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub>  
Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>  
Ser-Z<sub>2</sub>;

Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently Pro,  
homoproline, thioproline, or  
N-methylalalanine; and

Z<sub>2</sub> is -OH or -NH<sub>2</sub>;

provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>, Xaa<sub>10</sub>,  
Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>, Xaa<sub>20</sub>, Xaa<sub>21</sub>,  
Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub>, and Xaa<sub>28</sub> are Ala; and provided that, if  
Xaa<sub>1</sub> is His, Arg or Tyr, then at least one of Xaa<sub>3</sub>, Xaa<sub>4</sub> and Xaa<sub>9</sub>  
is Ala; and pharmaceutically acceptable salts thereof;

30. A compound according to claim 29 which has an amino  
acid sequence selected from SEQ. ID. NOS. 5-9.

31. A composition comprising a compound of any of claims 1  
to 29 in a pharmaceutically acceptable carrier.

32. A composition comprising a compound of claim 30 in a  
pharmaceutically acceptable carrier.

33. A method for the treatment of diabetes mellitus  
comprising the administration of a therapeutically effective  
amount of a compound according to claim 1.

34. A method for the treatment of diabetes mellitus  
comprising the administration of a therapeutically effective  
amount of a compound according to claim 28.

35. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 29.

36. The method of claim 33 further comprising the administration of a therapeutically effective amount of an insulin.

37. The method of claim 34 further comprising the administration of a therapeutically effective amount of an insulin.

38. The method of claim 35 further comprising the administration of a therapeutically effective amount of an insulin.

39. A method for the treatment of a hyperglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 1.

40. A method for the treatment of a hyperglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 28.

41. A method for the treatment of a hypoglycemic condition in a mammal comprising the step of administering a



therapeutically effective amount of a compound according to claim 29.

42. A peptide compound of the formula (II) [SEQ. ID. NO. 94]:

Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Ala Xaa<sub>19</sub> Xaa<sub>20</sub>  
Xaa<sub>21</sub> Xaa<sub>22</sub> Xaa<sub>23</sub> Xaa<sub>24</sub> Xaa<sub>25</sub> Xaa<sub>26</sub> X<sub>1-Z<sub>1</sub></sub>; wherein

Xaa<sub>1</sub> is His, Arg, Tyr, Ala, Norval, Val, Norleu or 4-imidazopropionyl;

Xaa<sub>2</sub> is Ser, Gly, Ala or Thr;

Xaa<sub>3</sub> is Ala, Asp or Glu;

Xaa<sub>4</sub> is Ala, Norval, Val, Norleu or Gly;

Xaa<sub>5</sub> is Ala or Thr;

Xaa<sub>6</sub> is Phe, Tyr or naphthylalanine;

Xaa<sub>7</sub> is Thr or Ser;

Xaa<sub>8</sub> is Ala, Ser or Thr;

Xaa<sub>9</sub> is Ala, Norval, Val, Norleu, Asp or Glu;

Xaa<sub>10</sub> is Ala, Leu, Ile, Val, pentylglycine or Met;

Xaa<sub>11</sub> is Ala or Ser;

Xaa<sub>12</sub> is Ala or Lys;

Xaa<sub>13</sub> is Ala or Gln;

Xaa<sub>14</sub> is Ala, Leu, Ile, pentyglycine, Val or Met;

Xaa<sub>15</sub> is Ala or Glu;

Xaa<sub>16</sub> is Ala or Glu;

Xaa<sub>17</sub> is Ala or Glu;

Xaa<sub>19</sub> is Ala or Val;

Xaa<sub>20</sub> is Ala or Arg;

Xaa<sub>21</sub> is Lys-NH<sup>e</sup>-R where R is Lys, Arg, C<sub>1</sub>-C<sub>10</sub> straight chain or branched alkanoyl or cycloalkyl alkanoyl Ala, Leu or;

Xaa<sub>22</sub> is Phe, Tyr or naphthylalanine;

Xaa<sub>23</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;

Xaa<sub>24</sub> is Ala, Glu or Asp;

Xaa<sub>25</sub> is Ala, Trp, Phe, Tyr or naphthylalanine;

Xaa<sub>26</sub> is Ala or Leu;

X<sub>1</sub> is Lys Asn, Asn Lys, Lys-NH<sup>e</sup>-R Asn, Asn Lys-NH<sup>e</sup>-R, Lys-NH<sup>e</sup>-R Ala, Ala Lys-NH<sup>e</sup>-R where R is Lys, Arg, C<sub>1</sub>-C<sub>10</sub> straight chain or branched alkanoyl or cycloalkylalkanoyl

Z<sub>1</sub> is -OH,

-NH<sub>2</sub>,

Gly-Z<sub>2</sub>,

Gly Gly-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub> or

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub> Xaa<sub>39</sub>-Z<sub>2</sub>;

wherein

Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from the group consisting of Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine and N-alkylalanine; and

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$Z_2$  is -OH or -NH<sub>2</sub>.

provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>4</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>, Xaa<sub>9</sub>, Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>, Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, are Ala; and provided also that, if Xaa<sub>1</sub> is His, Arg, Tyr, or 4-imidazopropionyl then at least one of Xaa<sub>3</sub>, Xaa<sub>4</sub> and Xaa<sub>9</sub> is Ala; and pharmaceutically acceptable salts thereof.

43. A compound according to claim 42 wherein Xaa<sub>1</sub> is His, Ala, Norval or 4-imidazopropionyl.

44. A compound according to claim 43 wherein Xaa<sub>1</sub> is His or 4-imidazopropionyl.

45. A compound according to claim 43 wherein Xaa<sub>1</sub> is Ala.

46. A compound according to claim 43 wherein Xaa<sub>1</sub> is His.

47. A compound according to claim 43 wherein Xaa<sub>1</sub> is 4-imidazopropionyl.

48. A compound according to claim 42 wherein Xaa<sub>2</sub> is Gly.

49. A compound according to any of claims 43-47 wherein Xaa<sub>2</sub> is Gly.

50. A compound according to claim 42 wherein Xaa<sub>3</sub> is Ala.

51. A compound according to any of claims 43-47 where Xaa<sub>3</sub> is Ala.

52. A compound according to claim 42 wherein Xaa<sub>4</sub> is Ala.
53. A compound according to any of claims 43-47 where Xaa<sub>4</sub> is Ala.
54. A compound according to claim 42 wherein Xaa<sub>9</sub> is Ala.
55. A compound according to any of claim 43-47 where Xaa<sub>9</sub> is Ala.
56. A compound according to claim 42 wherein Xaa<sub>14</sub> is Leu, pentylglycine or Met.
57. A compound according to claim 42 wherein Xaa<sub>25</sub> is Trp or Phe.
58. A compound according to claim 42 wherein Xaa<sub>6</sub> is Ala, Phe or naphthylalanine; Xaa<sub>22</sub> is Phe or naphthylalanine; and Xaa<sub>23</sub> is Ile or Val.
59. A compound according to claim 42 wherein Z<sub>1</sub> is -NH<sub>2</sub>.
60. A compound according to claim 42 wherein Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.
61. A compound according to claim 42 wherein Xaa<sub>39</sub> is Ser or Tyr.

62. A compound according to claim 58 wherein Xaa<sub>39</sub> is Ser or Tyr.

63. A compound according to claim 42 wherein Xaa<sub>39</sub> is Ser.

64. A compound according to claim 58 wherein Xaa<sub>39</sub> is Ser.

65. A compound according to claim 42 wherein Z<sub>2</sub> is -NH<sub>2</sub>.

66. A compound according to any of claims 50, 52 or 54 wherein Z<sub>2</sub> is -NH<sub>2</sub>.

67. A compound according to claim 42 wherein Z<sub>1</sub> is -NH<sub>2</sub>.

68. A compound according to claim 42 wherein Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

69. A compound according to claim 42 wherein X<sub>1</sub> is Lys Asn, Lys-NH<sup>e</sup>-R Asn, or Lys-NH<sup>e</sup>-R Ala where R is Lys, Arg, C<sub>1</sub>-C<sub>10</sub> straight chain or branched alkanoyl.

70. A compound according to claim 42 wherein Xaa<sub>21</sub> is Lys-NH<sup>e</sup>-R where R is Lys, Arg, C<sub>1</sub>-C<sub>10</sub> straight chain or branched alkanoyl or cycloalkyl-alkanoyl

72. A composition comprising a compound of claim 42 in a pharmaceutically acceptable carrier.

73. A composition comprising a compound of claim 71 in a pharmaceutically acceptable carrier.

1. The first step is to identify the problem or question that needs to be addressed. This involves understanding the context and the specific requirements of the task.